7 March 2013
EMA/162000/2013
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 4-7 February 2013

Chair: June Raine – Vice-Chair: Almath Spooner

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1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

The Chairperson opened the meeting and welcomed all participants to the 4-7 February 2013 meeting of the PRAC.

Based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some Committee members for the upcoming discussions; in accordance with the Agency's policy on the handling of conflicts of interests, participants in this meeting were asked to declare any changes, omissions or errors to the already declared interests on the matters for discussion (see Annex II). No new or additional conflicts were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 22 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Adoption of the agenda of the PRAC meeting on 4-7 February 2013

The agenda was adopted with the addition of the following topics upon request from the members of the Committee and the EMA secretariat: 2.1.1. Cyproterone, ethinylestradiol – DIANE 35 & generics; 3.2.1. Hydroxyethyl starch, solutions for infusion; 11.11.1. Implementation of the pharmacovigilance legislation; 12.1. Overview of progressive multifocal leukoencephalopathy (PML) in EudraVigilance.

In line with the principles agreed at the PRAC 7-10 January 2013 meeting, some risk management plans were identified as suitable for endorsement of the conclusion of the PRAC Rapporteur assessment without discussion at the meeting. These decisions are duly recorded in the minutes under the individual topics.

1.3. Adoption of the minutes of the previous PRAC meeting on 7-10 January 2013

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the minutes were published on 25 February 2013 on the EMA website

2. EU Referral Procedures for Safety Reasons: Urgent EU Procedures

2.1. Newly triggered procedures

2.1.1. Cyproterone, ethinylestradiol – DIANE 35 & other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms (NAPs)

- Review of the benefit-risk balance following notification by France of a referral under Article 107i of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)
PRAC Co-Rapporteur: Evelyne Falip (FR)

Background

The French medicines agency (ASNM) sent a letter of notification dated 4/2/2013 triggering a referral under Article 107i of Directive 2001/83/EC for Diane 35 and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms, following their decision to suspend Diane 35 and its generics in France within three months due to reports of venous and arterial thromboembolism and concerns relating to off-label use in France.

Discussion

The PRAC noted the notification letter from the French Medicines Agency and discussed the list of questions to be addressed during the procedure as well as a timetable for conducting the review.

The PRAC appointed Sabine Straus (NL) as Rapporteur and Evelyne Falip (FR) as Co-Rapporteur for the procedure.

Summary of recommendation(s) / conclusions

The PRAC adopted a list of questions to be addressed by the marketing authorisation holders (MAHs), (EMA/PRAC/69149/2013) published on the EMA website and by the stakeholders (EMA/PRAC/78185/2013) and a timetable for the procedure (EMA/PRAC/69142/2013).

2.2. Ongoing Procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

3. EU Referral Procedures for Safety Reasons: Other EU Referral Procedures

3.1. Newly triggered Procedures

3.1.1. Combined hormonal contraceptives: desogestrel, gestodene, norgestimate, etonogestrel, drospirenone, dienogest, chlormadinone, norgestimate (NAPs), nomegestrol acetate / estradiol – IOA (CAP), ZOELY (CAP), norelgestromin / ethinylestradiol - EVRA (CAP)

- Review of the benefit-risk balance of combined hormonal contraceptives based on pharmacovigilance data following notification by France of a referral under Article 31 of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

PRAC Co-Rapporteur: Evelyne Falip (FR)

Background

The French Medicines Agency (ANSM) sent a letter of notification dated 5/2/2013 of a referral under Article 31 of Directive 2001/83/EC for the review of combined hormonal contraceptives following concerns in France about the known risk of venous thromboembolism.

Discussion

The PRAC noted the letter of notification from the French medicines agency and discussed a list of questions to be addressed during the procedure as well as a timetable for conducting the review. The PRAC noted that the EMA secretariat will also contribute to the procedure gathering additional scientific evidence for supporting decision making.

The PRAC appointed Julie Williams (UK) as Rapporteur and Evelyne Falip (FR) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (EMA/PRAC/60232/2013) and a timetable for the procedure (EMA/PRAC/60281/2013-Rev).

3.2. Ongoing Procedures

3.2.1. **Hydroxyethyl starch** (**HES**), **solutions for infusion** (NAPs)

- Ongoing review of the risk/benefit balance of HES-containing products under referral Article 31 of Directive 2001/83/EC based on pharmacovigilance data.

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
PRAC Co-Rapporteur: Martin Huber (DE)

Background

A referral procedure under Article 31 is ongoing for hydroxyethyl starch (HES), solutions for infusion in the management of hypovolaemia and hypovolaemic shock in critically ill / intensive care unit (ICU) patients and, in particular, in patients with sepsis.

The PRAC was informed of the intention expressed by one of the MAHs concerned, to amend the product information for their HES-containing products via a variation in the relevant Member States. This follows the results of a post-hoc analysis of a subgroup of the Effects of Voluven on Hemodynamics and Tolerability of Enteral Nutrition in Patients With Severe Sepsis (CRYSTMAS) trial.

Given the ongoing referral procedure, the PRAC was presented with the preliminary results of the post-hoc analysis and with the rationale to amend the product information. The PRAC was also informed of the recently updated International Guidelines for Management of Severe Sepsis and Septic Shock (Surviving Sepsis Campaign)[1].

[1]. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012.

Summary of recommendation(s)/conclusions

The PRAC noted the limitations of the preliminary results of the post-hoc analysis, as presented by the (co-)Rapporteurs of the referral procedure. The PRAC took note of the recently issued updated international guidelines.

The PRAC agreed that whilst the results of this post-hoc analysis remained to be assessed as part of the MAHs responses to the PRAC LoQ for the Art. 31 referral (assessment report due by 8 April), there were no scientifically justified grounds for a shortened assessment to be performed at this stage, nor for additional questions to be posed to the MAHs. The PRAC also agreed that the issue required careful consideration and input from experts in this field. Consultation on the subject with an ad-hoc expert group meeting was considered appropriate. Such a group should be convened to allow full understanding of the evidence and support the PRAC in its final decision on the Art.31 referral. Practicalities will be discussed at the next PRAC discussion on the procedure.

3.3. Procedures for finalisation

None

3.4. Article 5(3) of Regulation (EC) No 726/2004 as amended: PRAC advice on CHMP request

None

3.5. Follow-up on finalised procedures

3.5.1. Nicotinic acid / laropiprant – **PELZONT** (CAP)**, TREDAPTIVE** (CAP)**, TREVACLYN** (CAP)

- Follow-up of finalised referral under Article 20(8) of Regulation (EC) No 726/2004 following procedural steps of Article 107i of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)
PRAC Co-Rapporteur: Menno van der Elst (NL)

Background

A preliminary discussion took place at the January 2013 PRAC to determine whether the safety concerns observed for the combination products containing nicotinic acid and laropiprant, would also be relevant to other mono-component medicinal products containing nicotinic acid or analogues thereof, with the same clinical indications. A non-urgent request of information (NUI) was sent to identify potentially relevant products.

Summary of recommendation(s)/conclusions

The results of the NUI were presented. The PRAC considered that products containing nicotinic acid or analogues thereof indicated in the treatment of lipid disorders should be reviewed. Further discussion will take place at the 4-7 March 2013 PRAC meeting.

Intensive Care Med. 2013 Feb;39(2):165-228. doi: 10.1007/s00134-012-2769-8. Epub 2013 Jan 30.

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Basiliximab – SIMULECT** (CAP)

- Signal of cardiovascular instability resulting in fatal outcome following off-label use in heart transplantation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Basiliximab is a monoclonal antibody authorised in the prophylaxis of acute kidney transplant rejection in de novo renal transplantation.

Simulect, a centrally authorised medicine containing basiliximab, is estimated to have been used by more than 430,000 patients worldwide, in the period from 1998 to 2012.

During routine signal detection activities, a signal of cardiovascular instability triggered by 3 cases with a fatal outcome following off-label use in heart transplantation was identified by the Swedish Medicines Agency. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reported. Since some factors such as underlying diseases and surgical procedures could have been considered as confounders, the PRAC agreed that some aspects needed further investigation. Moreover, a further search in EudraVigilance identified cases of cardiac failure and cardiac arrest in temporal association with the use of basiliximab when the medicine was used within its authorised indication. Therefore, the PRAC agreed that the signal needed further investigation.

Summary of recommendation(s)

- The MAH for Simulect (basiliximab) should be requested to submit to the EMA, within 60 days, a cumulative review of the signal addressing a number of points requested by the PRAC, including information on all the cases associated with the use of basiliximab and related terms, follow-up of the reported cases as well as pre-clinical evidence, and an explanation of a possible biological mechanism. The different patterns of utilisation of basiliximab should be taken into account in this review, given its use outside the authorised indication.
- A 30 day timetable was supported to assess the results of this review, leading to a further PRAC recommendation.

4.1.2. **Tramadol** (NAP)

- Signal of hypoglycaemia

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Tramadol is a centrally acting analgesic used in the treatment of moderate to severe pain, alone or in combination with other substances such as paracetamol. Medicines containing tramadol are very widely used worldwide.

A signal of hypoglycaemia was identified by the French Medicines Agency (ASNM), from the French National Survey on tramadol adverse drug reactions covering the period from 1 August 2010 to 31 July 2011. This survey was initiated following the withdrawal of dextropropoxyphene-containing medicines[2] in France, in order to monitor potential risks related to the increased prescription of tramadol. The signal was based on cumulative data gathered up to 2012 including cases identified in the French pharmacovigilance database and other cases reported to the MAH worldwide. FR confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information from reported cases of hypoglycaemia and data from the literature. The PRAC noted that some cases involved the combination with paracetamol and that some scientific articles supported a plausible biological mechanism. Therefore the PRAC agreed that the signal needed further investigation.

The PRAC appointed Isabelle Robine as Rapporteur for the assessment of the review.

Summary of recommendation(s)

- The MAH for the innovator tramadol-containing medicines should be requested to submit to the PRAC Rapporteur, within 60 days, an update of the previously finalised 'cumulative scientific evaluation of an association between hypoglycaemia and tramadol-containing medicinal products' with additional data available up to January 2013[3].

4.2. New signals detected from other sources

4.2.1. Ticagrelor – **BRILIQUE** (CAP)**, POSSIA** (CAP)

- Signal of food interaction with grapefruit juice

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Ticagrelor is an adenosine diphosphate (ADP) receptor antagonist authorised in the prevention of atherothrombotic events in patients with acute coronary syndromes.

The exposure for Brilique and Possia, centrally authorised medicines containing ticagrelor, is estimated to have been almost 40,000 patient-years worldwide, in the period from first authorisation in 2010 to 2012. During routine signal detection activities, a signal of interaction with grapefruit juice was

[2] See European Medicines Agency recommends withdrawal of dextropropoxyphene-containing medicines 2009
[3] In the framework of a follow-up of a previous review conducted under a PSUR work-sharing procedure finalised in November 2012

identified by the EMA, based on an article published in the British Journal of Clinical Pharmacology[4]. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the results of the randomized, cross-over pharmacokinetic drug-interaction study described in the article, involving ten healthy volunteers and suggesting that grapefruit juice markedly increases the plasma concentrations and antiplatelet effects of ticagrelor in healthy subjects.

The PRAC noted that a subsequent search performed in EudraVigilance did not retrieve any cases with information suggestive of an interaction. Nevertheless the effects of co-administration of strong and moderate CYP3A4 inhibitors on the pharmacokinetic properties of ticagrelor are known and described in the product information. Therefore the PRAC concluded that the evidence arising from this clinical study provided sufficient grounds to warrant an amendment of the product information to inform prescribers and patients/consumers of the potential interaction between ticagrelor and grapefruit juice.

Summary of recommendation(s)

- The MAH for Brilique/Possia (ticagrelor) should be requested to submit to the EMA, within 60 days, a variation including a proposal for amending the product information[5] in order to address the signal.

4.2.2. Thiocolchicoside (NAP)

- Signal of potential genotoxicity

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Thiocolchicoside is a semi-syntetic sulfuraded colchicoside derivative used as a muscle relaxant.

Following pre-clinical study results that became available for thiocolchicoside -in 2009, the Italian Medicines Agency requested the MAH to perform studies to investigate the potential for genotoxicity for thiocolchicoside and some of its metabolites.

Two pre-clinical studies were performed and after assessing the results, IT considered these as a signal for initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the results of the pre-clinical studies consisting of an in-vitro micronucleus test in human leukocytes and in-vivo tests in rat bone marrow, which could be linked to aneugenic potential of one of the metabolites. The risk associated with aneuploidy in humans was evaluated by the Italian Medicines Agency. The PRAC agreed that there was a lack of information on whether the aneugenic effect could be considered dose-dependent or not.

[4] Holmberg MT, Tornio A, Joutsi-Korhonen L, Neuvonen M, Neuvonen PJ, Lassila R, Niemi M, Backman JT.Grapefruit juice markedly increases the plasma concentrations and antiplatelet effects of ticagrelor in healthy subjects. Br J Clin Pharmacol. 2012 Nov 6. doi: 10.1111/bcp.12026. [Epub ahead of print]

[5] Section 4.5 of the SmPC and 1 - Taking Brilique with food and drink - in the PL

The PRAC discussed the possible risk minimisation measures to address this signal and agreed that the further review of the available data was required in order to determine the impact of these results for clinical use. In addition more data are needed for a better characterisation of the risk, and,these should be gathered in the context of a full benefit-risk analysis.

Summary of recommendation(s)

- The MSs should consider a full review of the benefit-risk balance of thiocolchicoside in the authorised indications.
- A non-urgent referral procedure should be considered as a suitable regulatory framework to perform this review.

Post-meeting note: at its 18-21 February 2013 meeting the CHMP noted the notification from IT triggering a referral procedure under Article 31 of Directive 2001/83/EC for thiocolchicoside-containing medicines (see 'Start of Community review' CHMP meeting of 18-21 February 2013 EMA/110776/2013).

4.2.3. Tolvaptan - SAMSCA (CAP)

- Signal of serious liver injury associated with high dose tolvaptan in patients with polycystic kidney disease

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Tolvaptan is a vasopressin V2-receptor antagonist used in the treatment of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). In some non-EU countries (including the USA), medicines containing tolvaptan have also been authorised to treat hyponatraemia due to heart failure or cirrhosis of the liver.

The exposure for Samsca, a centrally authorised medicine containing tolvaptan, is estimated to have been around 1,800 patient-years worldwide, in the period from 2011 to 2012.

In a recent clinical trial, TEMPO[6], conducted in the USA in about 1,400 patients with autosomal dominant polycystic kidney disease (ADPKD), an increased risk of serious liver injury in patients receiving tolvaptan (4.4%) compared with placebo (1.0%) had been identified. In addition across the clinical trial database three patients treated with 120mg/d tolvaptan developed significant increases (meeting Hy's law criteria) in serum alanine aminotransferase (ALT) and concomitantly clinically significant increases in bilirubin within the first 18 months of treatment. Symptoms improved upon discontinuation of tolvaptan. These results were also reported in a 'Safety Alert from the FDA on potential risk of liver injury'. The Rapporteur reviewed these findings and confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the results of the study. The PRAC noted that ADPKD is not an authorised indication in either the US or the EU, and that the posology used in the study differed from the authorised one in the EU. Similar concerns had not been identified in clinical trials conducted in support

[6] Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes

of the currently authorised indications either in the EU or the US. A search in EudraVigilance identified a total of 13 cases of hepatic adverse drug reactions. the PRAC agreed that the cases reported in the clinical trial TEMPO suggested a likely causal association with the treatment. Therefore further investigation as regards any potential risk for patients treated in the authorised indication and posology is warranted and prescribers should be adequately informed.

Summary of recommendation(s)

- The MAH for Samsca (tolvaptan) should be requested to submit to the EMA within 30 days, in the framework of a variation, further data and a cumulative review of the signal, together with a proposal for amending the product information as well as a proposal for a DHPC and communication plan.

4.2.4. **Zolpidem** (NAP)

- Signal of impaired mental alertness next morning, including impaired driving ability

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Zolpidem is a hypnotic agent used for short-term treatment of insomnia.

Following a Drug Safety Communication from the FDA on 'Lower Recommended Doses of Zolpidem Containing Products', Italy (IT) – as lead MS for the signal management activities for zolpidem in the EU – performed a search in EudraVigilance of cases associated with zolpidem and impaired driving ability as well as road traffic accidents[7], and considered that a signal of impaired mental alertness next morning, including impaired driving ability, needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases retrieved from EudraVigilance as well as a possible biological rationale for these reactions. The PRAC noted that the vast majority of the cases had been reported in the USA. The PRAC also noted that residual somnolence, somnambulism and impaired driving ability are already listed as undesirable effects and in special warnings in zolpidem product information, along with warnings that patients may still feel drowsy the morning after taking these products.

However, the PRAC recognised that information on dosages for the cases reported was lacking and specific review of information on pharmacokinetic data, especially in taking into consideration possible sex differences, differences in liver function and in the elderly, would help in considering further risk minimisation activities, particularly in relation to posology and dose.

The PRAC appointed Carmela Macchiarulo (IT) as Rapporteur for the assessment of the review.

Summary of recommendation(s)

- The MAH for the originator zolpidem-containing medicine should be requested to submit within 60 days a cumulative review of the signal to the PRAC Rapporteur, including an analysis of all case reports of 'impaired driving ability', 'road traffic accident', and 'somnambulism' associated

[7] MedDRA preferred terms

with zolpidem and, as appropriate, a proposal for amending the product information and further pharmacovigilance activities. In addition, the MAH should provide an overview of pharmacokinetic data, taking into consideration possible sex differences.

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up

4.3.1. **Domperidone** (NAP)

- Signal of cardiotoxicity

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné

Background

Domperidone is a prokinetic agent and a dopamine antagonist with antiemetic properties. Medicines containing domperidone are widely used for the relief of nausea and vomiting and are available either Prescription-Only (POM) and/or Over-The-Counter (OTC) depending on the EU Member State where they are marketed.

In 2011 the Pharmacovigilance Working Party (PhVWP) discussed the risk of cardiac disorders associated with domperidone (see PhVWP October 2011 Monthly report).

The PhVWP agreed that the MAH should be requested to conduct a well-designed and powered epidemiological study to investigate the association between domperidone and cardiac disorders, with emphasis on dose-response. BE, as Reference Member State (RMS) for Motilium (domperidone), requested the MAH to conduct a 'thorough QTc study' in line with the International Conference on Harmonisation ICH E14 guideline. The results of this study are foreseen by the end of April 2013.

BE informed the PRAC of the new evidence that led to their current intention to change the marketing authorisation status of domperidone-containing medicines from OTC to POM in Belgium following the last 2011 discussion.

Discussion

The PRAC noted that between December 2011 and June 2012, the Belgian medicines agency (FAMHP) received 3 additional cases of serious cardiac disorders associated with domperidone use. Furthermore, during routine signal detection activities, BE found an increase in the proportional reporting ratio (PRR) for cardiac disorders. After preliminary assessment of the latest PSUR submitted, an additional contraindication for the use of domperidone in some patients was being considered. Based on the new evidence, the PRAC agreed on the need to fully review the benefit-risk of domperidone in the current indications.

Summary of recommendation(s)

- A full review of the benefit-risk of domperidone in the authorised indications should be considered by the MSs.
- Before any review is started, BE should gather further data on the legal status of domperidone-containing medicines as well as the indications, posology and off-label use in the EU by means of a non-urgent information request (NUI) to the MSs.

4.3.2. **Roxithromycin** (NAPs)

- Signal of hearing disorders

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

For background, see minutes of the PRAC 3-5 September 2012.

The MAH replied to the request for information on the signal of hearing disorders and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the data on the cases reported, including information on positive de-challenge and re-challenge, and agreed that the evidence was consistent with existing data for other macrolides, concluding that a possible relationship between roxithromycin administration and hearing disorders could not be ruled out. Therefore the PRAC agreed that the product information of roxithromycin-containing medicinal products should be amended to reflect this data. The PRAC noted that a type II variation procedure had already been submitted by the innovator for roxithromycin–containing medicines to the Italian Medicines Agency (AIFA).

Summary of recommendation(s)

- The MAHs for roxithromycin-containing medicines should be requested to submit within 60 days a variation to update the product information as regards the risk of hearing disorders[8] to the NCAs of the MSs[9].

4.3.3. **Roxithromycin** (NAP)

- Signal of rhabdomyolysis secondary to interaction with statins

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

For background, see minutes of the PRAC 3-5 September 2012.

The MAH replied to the request for information on the signal of rhabdomyolysis secondary to interaction with statins and the responses were assessed by the Rapporteur.

[8] SOC – Ear and vestibular disorders – section 4.8 of the SmPC and PL: ear and vestibular disorders: deafness transitory, hypoacusis, vertigo and tinnitus

[9] [10] In line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, the marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004 (EMA website). For nationally authorised medicines, it is the responsibility of the National Competent Authorities of the Member States to oversee that these recommendations are adhered to.

Discussion

The PRAC discussed the assessment of the clinical overview for roxithromycin on rhabdomyolysis with particular reference to interaction with statins as well as the results of an analysis performed by the EMA on EudraVigilance reports received for selected macrolides up to October 2012. It was noted that in the majority of the cases rhabdomyolysis occurred following the introduction of the antibiotic. The PRAC agreed that a biological rationale for the interaction was plausible – based on the inhibitory effect of roxithromycin on CYP3A4 and/or drug transporters like OATP1B1 and OATP1B3 leading to a possible increase of statin exposure. Furthermore it was noted that the potential for interaction is already known for other medicines belonging to the macrolide class. Therefore the PRAC agreed that the product information should be updated to reflect these data.

Summary of recommendation(s)

- The MAHs for roxithromycin-containing medicines should be requested to submit to the NCAs of the MSs[10] within 60 days a variation to update the product information as regards risk of rhabdomyolysis secondary to interaction with statins[11].

4.3.4. Sugammadex - BRIDION (CAP)

- Signal of bronchospasm and other respiratory symptoms

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Background

For background, see minutes of the PRAC 1-3 October 2012.

The MAH replied to the request for information on the signal of bronchospasm and other respiratory symptoms and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the cumulative review performed in relation to bronchospasm, respiratory obstruction and pulmonary oedema. The PRAC considered that the majority of the case reports reviewed provided insufficient information for evaluation, described concurrent symptoms that were typical of hypersensitivity reactions and/or reported underlying pulmonary complications. Therefore, based on the data presented, no new safety concern was identified with regard to respiratory adverse events.

On the other hand, the PRAC commented that based on this latest review the current product information could be expanded in relation to respiratory symptoms. In particular, the fact that bronchospasm and pulmonary obstructive events could be related to hypersensitivity should be emphasised.

[11] Section 4.5 of the SmPC: Interaction with other medicinal products and other forms of interaction:
HMG-CoA Reductase Inhibitors
When roxithromycin and an HMGCoA reductase inhibitor (statin) are combined, there is a potential risk of muscle related adverse events, such as rhabdomyolysis due to a possible increase of the statin exposure.
Caution should be exercised when a statin is combined with roxithromycin and patients should be monitored for signs and symptoms of myopathy.

Summary of recommendation(s)

- The MAH for Bridion (sugammadex) should be requested to update the product information as regards information available on bronchospasm and respiratory events[12]. Relevant changes should be reflected in the Risk Management Plan. Such changes should be considered in the framework of the ongoing procedure for the renewal of the marketing authorisation submitted to the EMA - see 9.2.3. .
- The MAH should closely monitor pulmonary obstructive events and submit to the EMA a cumulative review of new data since November 2012 in the next PSUR.

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

The PRAC provided advice to the CHMP on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation. Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

5.1.1. Alogliptin

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.2. Alogliptin, metformin

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.3. Alogliptin, pioglitazone

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.4. Autologous cultured chondrocytes

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.5. Autologous oral mucosal epithelial cells

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.6. Dimethyl Fumarate

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.7. Imatinib

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.8. Indacaterol maleate, glycopyrronium bromide

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

[12] The paragraph 'Drug hypersensitivity' in section 4.8 of the SmPC should be amended to include 'bronchospasm' and 'obstructive events'. The paragraph 'Pulmonary patients' in section 4.8 should be updated with further clinical and post-marketing data. Current information: "one clinical trial …in two patients" should be expanded.

5.1.9. Influenza Vaccine (tetravalent live attenuated, nasal)

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.10. Lomitapide

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.11. Lurasidone

- Evaluation of a RMP in the context of an initial Marketing Authorisation Application procedure

5.1.12. Perflubutane

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.13. Tobramycin

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.2. Medicines already authorised

RMP in the context of a PSUR procedure

5.2.1. Axitinib – **INLYTA** (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of this updated version 6 of the RMP for the above mentioned medicine.

See also 6.4.

5.2.2. Dronedarone – **MULTAQ** (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of this updated version 7 of the RMP for the above mentioned medicine.

See also 6.9.

5.2.3. Epoetin Theta – **BIOPOIN** (CAP)**, EPORATIO** (CAP)

- Evaluation of RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Epoetin theta is a recombinant epoetin used in the treatment of symptomatic anaemia associated with chronic renal failure in adult patients and of symptomatic anaemia in adult cancer patients with non-myeloid malignancies.

The PRAC is responsible for providing advice to the CHMP on the cumulatively assessed versions 7, 8, 9 and on version 10 including updates to the RMP following assessment of the accompanying PSUR for Biopoin and Eporatio, centrally authorised products containing epoetin theta.

Summary of advice

- The updated RMP version 10 for Biopoin and Eporatio (epoetin theta) was considered acceptable provided that the MAH submits within 30 days a further update in order to discuss preliminary results of the study XM01-23 (study on the use of epoetin theta in the treatment of anaemia in cancer patients receiving chemotherapy including patients with multiple myeloma, low-grade non-Hodgkin's lymphoma or chronic lymphocytic leukaemia and with endogenous erythropoietin deficiency), taking into account some clarifications requested by the PRAC.

In the context of the discussion, the PRAC noted that in 2007(EMEA/496188/2007) and 2008 (EMEA/CHMP/333962/2008), the CHMP considered that there was a need to increase the scientific knowledge on epoetins regarding their impact on the survival of anaemic patients receiving chemotherapy and recommended to perform additional studies to clarify the benefits and risks in this group of patients. EMA will plan further discussion on this aspect by presenting a progress report on this for the April and May 2013 PRAC meetings.

See also 6.10.

5.2.4. Fampridine – FAMPYRA (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Fampyra, containing fampridine, is a potassium channel blocker indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7).

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Fampyra.

Summary of advice

- The updated RMPs version 6 for Fampyra (fampridine) was considered acceptable provided that the MAH responds to a list of questions agreed by the PRAC including clarification of the protocol of the planned PASS, particularly the aspects relating to drug utilisation, and on the pregnancy registry.

See also 6.11.

5.2.5. Methoxy polyethylene glycolepoetin beta – MIRCERA (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Background

Mircera, a centrally authorised medicine containing methoxy polyethylene glycolepoetin beta (epoetin beta bound to methoxy polyethylene glycol butanoic acid) is a recombinant epoetin indicated in the treatment of symptomatic anaemia associated with chronic kidney disease.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Mircera.

Summary of advice

- The updated RMPs version 10 for Mircera (methoxy polyethylene glycolepoetin beta) was considered acceptable.

See also 6.15.

5.2.6. Orlistat – ALLI (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 12 of the RMP for the above mentioned medicine.

See also 6.17.

5.2.7. Ribavirin – REBETOL (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

The PRAC endorsed the conclusions of the Rapporteur assessment of the version 3 of the RMP for the above mentioned medicine.

See also 6.24.

5.2.8. Romiplostim – NPLATE (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 11 of the RMP for the above mentioned medicine, provided in the framework of a common assessment with the accompanying PSUR.

See also 6.25.

5.2.9. Rotavirus vaccine, live, attenuated – ROTARIX (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogne (BE)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 7 of the RMP for the above mentioned medicine.

See also 6.26.

5.2.10. Saxagliptin – ONGLYZA (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 2 of the RMP for the above mentioned medicine. The MAH was requested to submit an updated version of the RMP within three months following a CHMP opinion on 17 January 2013 on a work-sharing procedure to address some minor changes requested by the Rapporteur.

See also 6.27.

5.2.11. Sitagliptin, metformin – EFFICIB (CAP), JANUMET (CAP), RISTFOR (CAP), VELMETIA (CAP)

- Evaluation of an RMP in the context of PSUR procedures

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 4.1 of the RMP for the above mentioned medicine.

See also 6.28.

RMP in the context of a variation

5.2.12. Agomelatine – THYMANAX (CAP), VALDOXAN (CAP)

- Evaluation of an RMP in the context of type II variations

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 14 of the RMP for the above mentioned medicine.

5.2.13. Belatacept – NULOJIX (CAP)

- Evaluation of an RMP in the context of a type II variation

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Belatacept is a fusion protein used, in combination with corticosteroids and mycophenolic acid, as prophylaxis against graft rejection in adults receiving a renal transplant.

The CHMP is evaluating a type II variation procedure for Nulojix, a centrally authorised product containing belatacept, to add information about cases of acute rejection when, in certain conditions, more rapid corticosteroid tapering had been used. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 9 for Nulojix (belatacept) in the context of the variation under evaluation by the CHMP was considered acceptable
- The PRAC supported a DHPC to inform prescribers of the increased rate of acute rejection with rapid corticosteroid tapering in patients with one or more risk factors for acute rejection, as well as update of the product information..

5.2.14. Bortezomib – VELCADE (CAP)

- Evaluation of an RMP in the context of a type II variation

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

For background, see PRAC minutes 29-31 October 2012.

At the 29-31 October meeting the PRAC decided to postpone the approval of the RMP for bortezomib (Velcade) given that the PRAC considered that more information was necessary to conclude whether inclusion of progressive multifocal leukoencephalopathy (PML) as an identified risk in the RMP was supported by the available evidence.

Further information was assessed by the Rapporteur following a response to a request for supplementary information from the MAH. In the context of this procedure the PRAC discussed the development of an overall strategy for the inclusion of information on the risk of PML in the RMP and product information for medicines used in populations where at increased risk, according to evidence based criteria. This will be considered further in a future meeting.

Summary of advice

- The RMP version 9 for Velcade (bortezomib) was considered acceptable in the context of the variation under evaluation by the CHMP. However, pending the CHMP decision on this variation procedure and the outcome of the overall strategy on the risk of PML (see above), the following points should be taken into account in the next RMP update:
    - PML should remain in the RMP as an important potential risk.

- The pharmacovigilance plan section of the RMP should be updated by including a follow-up questionnaire to be used to gather more information on the individual PML cases, as recommended by the PRAC in the 29-31 October 2012 meeting.

- A monitoring program for PML should be proposed by the MAH. This program should, if implemented, be included in the RMP.

See also: 12.1.

5.2.15. Canakinumab – ILARIS (CAP)

- Evaluation of an RMP in the context of a type II variation, extension of indication

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Canakinumab is a monoclonal antibody used in the treatment of cryopyrin-associated periodic syndromes (CAPS).

The CHMP is evaluating an extension of the therapeutic indication for Ilaris, a centrally authorised product containing canakinumab, to include the treatment of active systemic juvenile idiopathic arthritis (SJIA) in selected patients. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 7 for Ilaris (canakimumab) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable provided that responses to a list of questions agreed by the PRAC are submitted before finalisation of the variation procedure by the CHMP.

5.2.16. Daranuvir – PREZISTA (CAP)

- Evaluation of an RMP in the context of a type II variation, extension of indication

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Darunavir is an antiviral co-administered with low-dose ritonavir for the treatment of human immunodeficiency virus (HIV-1) in adult patients as well as antiretroviral therapy '(ART)-experienced' paediatric patients.

The CHMP is evaluating an extension of the therapeutic indication for Prezista, a centrally authorised product containing darunavir, to include the treatment of HIV-infected treatment-naive patients aged 12 to 18 years. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 16 for Prezista (darunavir) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable.
- The next update of the RMP should take into account some additions and clarifications requested by the PRAC with regards to growth abnormalities (to be included as an 'important potential risk'), and effects on lipid metabolism.

5.2.17. Fampridine – FAMPYRA (CAP)

- Evaluation of an RMP in the context of a type II variation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 5.2 of the RMP for the above mentioned medicine.

5.2.18. Golimumab – SIMPONI (CAP)

- Evaluation of an RMP in the context of a type II variation, extension of indication

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

For background, see minutes of the PRAC 1-3 October 2012.

Responses were received to the PRAC list of questions. The Rapporteur assessed the responses received for further PRAC advice.

Summary of advice[13]

- The updated RMP version 8 for Simponi (golimumab) submitted in the context of the variation under evaluation by the CHMP was considered acceptable provided that the outstanding point below is addressed before finalisation of the variation procedure by the CHMP.
- A disease registry in Inflammatory Bowel Diseases with the aim to follow up long-term safety of biologics, and with relevant comparisons to non-biologic treatments, should be required, as it is considered the best option to assess the long-term safety of golimumab in UC. This registry should allow comparison between different biological therapies, and with relevant comparisons to non-biologic treatments, and observation of switches between therapies. Thus, the MAH should continue to explore ways to achieve this goal. As a first step, a careful review of available options, and a proposal for a way forward should be submitted to the EMA.

5.2.19. Human Fibrinogen, human thrombin – EVICEL (CAP)

- Evaluation of an RMP in the context of a type II variation, extension of indication

[13] PRAC advice finalised via written procedure on 8 February 2013

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Evicel, a centrally authorised sealant solution containing human fibrinogen, human thrombin indicated as supportive treatment in surgery, for improvement of haemostasis where standard surgical techniques are insufficient.

The CHMP is evaluating an extension of the therapeutic indication for Evicel to include use in neurosurgical procedures. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP 12 for EVICEL (Human Fibrinogen and Human Thrombin) submitted in the context of the extension of indication under evaluation by the CHMP and versions 8 (see 5.2.30.) submitted as a stand-alone RMP were considered acceptable provided that some outstanding points requested by the PRAC are addressed before finalisation of the variation procedure by the CHMP. These include a proposal on educational material to be added to the RMP; clarification of the current status of the outstanding pharmacovigilance activities as outlined in the Article 20 of Regulation (EC) No 726/2004 decision; plans to assess the effectiveness of the risk minimisation measures (for air/ gas embolism) in the RMP; targeted follow-up of any report suggestive for gas embolism.

5.2.20. Insulin aspart – NOVORAPID (CAP)

- Evaluation of an RMP in the context of a type II variation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

The PRAC noted the conclusion of the type II variation assessment report that the applicant should prepare and submit a RMP for the substance according to the template published at the EMA website for good pharmacovigilance practices (GVP) Module V – Risk management systems. PRAC advice will be given upon submission. The PRAC endorsed the specific comments of the Rapporteur on the safety concerns related to the insulin pump device for the above mentioned medicine.

5.2.21. Leflunomide – LEFLUNOMIDE MEDAC (CAP)

- Evaluation of an RMP in the context of a type II variation, line extension

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 6 of the RMP for the above mentioned medicine.

5.2.22. Natalizumab – TYSABRI (CAP)

- Evaluation of an RMP in the context of a Type II variation, extension of indication

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Natalizumab is a monoclonal antibody used in the treatment of multiple sclerosis with high disease activity despite treatment with a beta-interferon.

The CHMP is evaluating an extension of the therapeutic indication for Tysabri, a centrally authorised product containing natalizumab, to include treatment in relapsing-remitting multiple sclerosis in a selected population without high disease activity who are anti-JCV-antibody negative. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 16 for Tysabri (natalizumab) submitted in the context of the extension of indication under evaluation by the CHMP was not considered acceptable since the proposed pharmacovigilance and risk minimisation activities were not judged to be sufficient to adequately manage the risk of PML in the newly proposed extension to the patient population (i.e. patients with relapsing remitting multiple sclerosis without high disease activity who are anti-JCV-antibody negative), especially in patients who experience JCV seroconversion. The MAH should be requested to submit an updated risk management plan and satisfactory responses to a list of questions agreed by the PRAC.

5.2.23. Velaglucerase alfa – VPRIV (CAP)

- Evaluation of an RMP in the context of a type II variation

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 7.0 and 7.1 of the RMP for the above mentioned medicine.

5.2.24. Sugammadex – BRIDION (CAP)

- Evaluation of an RMP in the context of a type II variation

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 6 of the RMP for the above mentioned medicine.

RMP in the context of a renewal of the marketing authorisation, conditional renewal or annual reassessment

5.2.25. Pazopanib – VOTRIENT (CAP)

- Evaluation of an RMP in the context of a conditional renewal procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 10 of the RMP as contained in the overall assessment produced for the renewal of MA as reported in 9.2.2.

5.2.26. Sugammadex – BRIDION (CAP)

- Evaluation of an RMP in the context of a renewal procedure

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 5 of the RMP as contained in the overall assessment produced for the renewal of the MA as reported in 9.2.3.

RMP in the context of a stand-alone RMP procedure

5.2.27. Dexamethasone – OZURDEX (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 1.9 of the RMP for the above mentioned medicine.

5.2.28. Fentanyl - INSTANYL (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 12 of the RMP for the above mentioned medicine.

5.2.29. Fesoterodine – TOVIAZ (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 7 of the RMP for the above mentioned medicine.

5.2.30. Human fibrinogen, human thrombin – EVICEL (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

The version RMP version 8 was assessed together with version 12 listed under point 5.2.19. , see above for the conclusions.

5.2.31. Hydroxycarbamide – SIKLOS (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogne (BE)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 13 of the RMP for the above mentioned medicine.

5.2.32. Ibandronic acid – BONDENZA (CAP), **BONDRONAT** (CAP), **BONVIVA** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 2 of the RMP for the above mentioned medicines.

5.2.33. Paliperidone – INVEGA (CAP), **XEPLION** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 3 of the RMP for the above mentioned medicines.

5.2.34. Pioglitazone – ACTOS (CAP), **GLUSTIN** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Background

Pioglitazone is a member of the thiazolidinedione class, used in the treatment of type II diabetes alone or in combination with other antidiabetic agents including metformin or glimepiride.

A number of centrally authorised products contain pioglitazone alone or in combination and the PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMPs for Actos and Glustin (pioglitazone), Tandemact (pioglitazone/glimepiride), Competact and Glubrava (pioglitazone/metformin), as well as for their centrally authorised generics.

Summary of advice

- The updated RMPs version 15.0 (Actos/Glustin), version 13 (Tandemact) and version 15 (Competact/Glubrava), pioglitazone (Actos/Glustin), pioglitazone/glimepiride (Tandemact), and pioglitazone/metformin (Competact/Glubrava) were considered acceptable.
- The next update of the RMPs for these products should take into account some clarifications requested by the PRAC and should be submitted to the EMA along with the next PSUR.

Post-meeting note: following proposal from the MAH the Rapporteur agreed that the next RMP update should be submitted following the assessment of the next PSUR (DLP 31 January 2013)

5.2.35. Pioglitazone – **GLIDIPION** (CAP), **PIOGLITAZONE ACTAVIS** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the RMP for the above mentioned medicines. Since these are generic products, their risk management plans have been aligned with that of the reference products Actos and Glustin (pioglitazone). See summary of advice 5.2.34.

5.2.36. Pioglitazone – **PAGLITAZ** (CAP), **PIOGLITAZONE KRKA** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the RMP for the above mentioned medicines. Since these are generic products, their risk management plans have beenaligned with that of the reference products Actos and Glustin (pioglitazone). See 5.2.34.

5.2.37. Pioglitazone – **PIOGLITAZONE TEVA** (CAP), **PIOGLITAZONE TEVA PHARMA** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the RMP for the above mentioned medicines. Since these are generic products, their risk management plans have been aligned with that of the reference products Actos and Glustin (pioglitazone). See 5.2.34.

5.2.38. Pioglitazone – **SEPIOGLIN** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the RMP for the above mentioned medicines. Since this is a generic product, its risk management plan has been aligned with that of the reference products Actos and Glustin (pioglitazone). See 5.2.34.

5.2.39. **Pioglitazone**, **glimepiride – TANDEMACT** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

See advice under 5.2.34.

5.2.40. **Pioglitazone**, **metformin – COMPETACT** (CAP), **GLUBRAVA** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

See advice under 5.2.34.

5.2.41. **Somatropin – NUTROPINAQ** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 2 of the RMP for the above mentioned medicines.

5.2.42. **Sunitinib – SUTENT** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 12 of the RMP for the above mentioned medicines.

5.2.43. **Tacrolimus – PROTOPIC** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 8 of the RMP for the above mentioned medicines.

5.2.44. Telmisartan, **hydrochlorothiazide – KINZALKOMB** (CAP), **MICARDISPLUS** (CAP), **PRITORPLUS** (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated version 8 of the RMP for the above mentioned medicines.

6. Assessment of Periodic Safety Update Reports (PSURs)

6.1. Agalsidase alfa – REPLAGAL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Agalsidase alfa is used to treat long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Replagal, a centrally authorised medicine containing agalsidase alfa, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Replagal (agalsidase alfa) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should continue to closely monitoring several ADRs including cardiac adverse events reported in relation to infusion-related reactions.
- The MAH is requested to provide additional assessment of the cardiac adverse events reported in relation to infusion-related reactions within 2 months.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.2. Aripiprazole – ABILIFY (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Margarida Guimaraes (PT)

Background

Aripiprazole is an antipsychotic used in the treatment of schizophrenia as well as in the treatment of moderate to severe manic episodes in bipolar I disorder and for the prevention of new manic episodes under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Abilify, a centrally authorised medicine containing aripiprazole, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Abilify (aripiprazole) in the approved indication(s) remains favourable.
- The PRAC recommended that the product information should be updated[14] to include serotonin syndrome and hepatic failure as new adverse drug reactions, to add the potential drug interaction associated with serotonin syndrome especially in cases of concomitant use with other serotonergic drugs such as SSRI/SNRI or with drugs that are known to increase aripiprazole concentrations, and to reflect the excretion of aripiprazole in human breast milk. Therefore the current terms of the marketing authorisation should be varied[15].
- In addition, the MAH should submit an updated RMP within 3 months to address the risk of serotonin syndrome and hepatic adverse events related to hepatic injury.
- Moreover, the MAH should submit to the EMA within three months all available further information relating to the excretion of aripiprazole in breast milk as well as a critical analysis of any effects on newborns following exposure to aripiprazole via the breast milk, including a comparison with other second-generation antipsychotics with regard to the available data and currently approved wording.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.3. Atazanavir – REYATAZ (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Atazanavir is a protease inhibitor used in the treatment of HIV infection.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Reyataz, a centrally authorised medicine containing atazanavir, and issued a recommendation on its marketing authorisation.

[14] SmPC sections 4.8, 4.5 and 4.6 respectively. The Package Leaflet should be updated accordingly.
[15] The PRAC Assessment Report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Reyataz (atazanavir) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should provide a comprehensive cumulative safety review on the risk of renal impairment with atazanavir based on the review of literature data and case reports, and provide cumulative qualitative and quantitative data on exposure in pregnancy.

The frequency of submission of PSURs should remain every three years and the next PSUR should be submitted to the EMA within 90 days of the data lock point.

6.4. Axitinib – INLYTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Axitinib is a protein kinase inhibitor used in the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Inlyta, a centrally authorised medicine containing axitinib, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Inlyta (axitinib) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The frequency of submission of PSURs should remain six-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.5. Corifollitropin alfa – ELONVA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Corifollitropin alfa is a sustained follicle stimulant used in controlled ovarian stimulation (COS) in combination with a GnRH antagonist for the development of multiple follicles in women participating in an assisted reproductive technology (ART) program.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Elonva, a centrally authorised medicine containing corifollitropin alfa, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Elonva (corifollitropin alfa) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should be changed from six monthly to once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.6. D-alfa-tocopherol – VEDROP (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

D-alfa-tocopherol is used in the treatment of vitamin E deficiency due to digestive malabsorption in paediatric patients with congenital chronic cholestasis or hereditary chronic cholestasis, from birth (full term newborns) up to 18 years of age.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Vedrop, a centrally authorised medicine containing d-alfa-tocopherol, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Vedrop (d-alfa-tocopherol) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH is requested to include: information on all Tanner score data collected and to provide a cumulative review of all cases of abnormal sexual and reproductive development reported; to provide a summary and discussion of the findings of the investigator initiated trials (Acanthocythosis (Switzerland) and chylomicron retention (Lyon France)).

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.7. Desloratidine, pseudoephedrine – AERINAZE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogne (BE)

Background

Desloratidine is a histamine antagonist and pseudoephedrine is a sympathomimetic agent. The combination desloratidine / pseudoephedrine is used for the symptomatic treatment of seasonal allergic rhinitis when accompanied by nasal congestion.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aerinaze, a centrally authorised medicine containing desloratidine and pseudoephedrine, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Aerinaze (desloratidine / pseudoephedrine) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should be changed from once yearly to every four years and the next PSUR should be submitted within 90 days of the data lock point.

6.8. Dexamethasone – OZURDEX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Ozurdex, is a centrally authorised product containing dexamethasone indicated for intravitreal use for the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO) and for the treatment of non-infectious uveitis affecting the posterior segment of the eye, branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ozurdex, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy and subject to updates of the safety information as detailed below, the risk-benefit balance of Ozurdex (dexamethasone) in the approved indication(s) remains favourable.
- The PRAC recommended that the product information[16] be updated to explicitly reflect that intravitreal injection of Ozurdex can be associated with ocular adverse reactions including retinal detachment. In addition, the product information should reflect revised instructions on the use of anti-microbial drops before, during and after. Therefore the current terms of the marketing authorisation should be varied[17].
- The MAH should include, within the next update of the RMP, the educational material covering more prescriptive instructions on the use of antimicrobial eye drops in line with the updated revised product information.

The frequency of submission of PSURs should remain six monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

[16] Sections 4.2, 4.4 and 4.8. The Package Leaflet updated accordingly.
[17] The PRAC Assessment Report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

6.9. Dronedarone – MULTAQ *(CAP)*

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Multaq, is a centrally authorised medicine containing dronedarone, an antiarrhythmic agent indicated for the maintenance of sinus rhythm after successful cardioversion in selected patients. Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Multaq, a centrally authorised medicine containing dronedarone, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Multaq (dronedarone) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should discuss cases of renal failure with possible de-challenge, as well as cases of pre-renal renal failure ,explain the impact on the safety profile of dronedarone; changes to the product information should be considered accordingly.

The frequency of submission of PSURs should remain six monthly and the next PSUR should be submitted within 70 days of the data lock point.

6.10. Epoetin Theta – BIOPOIN *(CAP)*, EPORATIO *(CAP)*

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

See also 5.2.3.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Biopoin and Eporatio, centrally authorised medicines containing epoetin theta, and issued a recommendation on their marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Biopoin and Eporatio (epoetin theta) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain 3 yearly and the next PSUR should be submitted within 90 days of the data lock point.

6.11. Fampridine – FAMPYRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Fampridine is a potassium channel blocker used for the improvement of walking in adult patients with multiple sclerosis with walking disability.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Fampyra, a centrally authorised medicine containing fampridine, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Fampyra (fampridine) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should provide a cumulative review of cases of seizure and should monitor differences in their distribution between different world regions. The MAH should also monitor cases of urinary tract infection and provide a cumulative analysis.

The frequency of submission of PSURs should remain six-monthly and the next PSUR should be submitted within 70 days of the data lock point.

6.12. Icatibant – FIRAZYR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Icatibant is an antagonist of bradykinin B2 receptors used in the treatment of acute attacks of hereditary angioedema (HAE) in patients with C1-esterase-inhibitor deficiency.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Firazyr, a centrally authorised medicine containing icatibant, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Firazyr (icatibant) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted within 70 days of the data lock point.

6.13. Idursulfase – ELAPRASE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Background

Elaprase a centrally authorised product containing idursulfase, an enzyme, indicated for the long-term treatment of patients with Hunter syndrome (mucopolysaccharidosis II, MPS II).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Elaprase and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Elaprase (idursulfase) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should provide a cumulative review and discussion of all reports of thrombocytopenia and of idiopathic thrombocytopenic purpura.

The frequency of submission of PSURs should remain yearly and the next PSUR should be submitted within 70 days of the data lock point; the EURD list should be updated accordingly.

6.14. Ioflupane (123 I) – DATSCAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Ioflupane (123 I), is a radiolabelled form of ioflupane, a cocaine analogue which binds to the presynaptic dopamine transporter of nerve cells.

Datscan, containing ioflupane, is a centrally authorised medicinal product indicated for diagnostic use indicated to detect loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain Parkinsonian syndromes.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Datscan, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Datscan (ioflupane (123 I)) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should be changed to every 5 years and the next PSUR should be submitted within 90 days of the data lock point.

6.15. Methoxy polyethylene glycolepoetin beta – MIRCERA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Background

Mircera, a centrally authorised methoxy polyethylene glycolepoetin beta (epoetin beta bound to methoxy polyethylene glycol butanoic acid) is a recombinant epoetin indicated in the treatment of symptomatic anaemia associated with chronic kidney disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mircera, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Mircera (methoxy polyethylene glycolepoetin beta) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should further characterise a number of adverse reactions under specific organ classes (SOCs).
- Moreover the MAH should be requested to continue investigating cases where neutralising anti-erythropoietin antibody-mediated pure red cell aplasia (AEAB-PRCA) cannot be ruled out and should continue to include the cumulative status update report in the PSUR.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.16. Nomegestrol, estradiol – IOA (CAP), ZOELY (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

The combination nomegestrol and estradiol is a combined oral contraceptive.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ioa and Zoely, centrally authorised medicines containing nomegestrol and estradiol, and issued a recommendation on their marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Ioa and Zoely (nomegestrol / estradiol) in the approved indication(s) remains favourable.

- The PRAC recommended that the product information be updated to reflect venous thrombo-embolic events and hypersensitivity reactions as undesirable effects. Therefore the current terms of the marketing authorisation should be varied[18].

In the context of the discussion the PRAC noted that the PASS study (CELINA) which is included in the RMP of the product, is a commitment of the MAH, and will allow the risk of venous thromboembolism (VTE) and arterial thromboembolism (ATE) to be better characterised. The study protocol is still under discussion. The PRAC is of the opinion that the study must start as soon as possible.

The frequency of submission of PSURs should remain six monthly and the next PSUR should be submitted within 70 days of the data lock point.

6.17. Orlistat – ALLI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Orlistat is a potent, specific and long-acting inhibitor of gastrointestinal lipases used in the treatment of obesity in adults who are overweight (body mass index, BMI, ≥28 kg/m^2) and should be taken in conjunction with a mildly hypocaloric, low-fat diet.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Alli, a centrally authorised medicine containing orlistat, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Alli (orlistat) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted within 70 days of the data lock point.

6.18. Palonosetron – ALOXI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Background

Palonosetron is a serotonin ($5HT_3$) antagonist used in the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy under certain conditions.

[18] The PRAC Assessment Report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aloxi, a centrally authorised medicine containing palonosetron, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Aloxi (palonosetron) in the approved indication(s) remains favourable.
- The PRAC recommended that the product information for Aloxi, 250 micrograms solution for injection be updated to reflect the adverse reaction "anaphylaxis, anaphylactic, anaphylactoid reactions and shock" with a frequency "very rare". In addition, the PRAC recommended that the product information for both, Aloxi 250 micrograms solution for injection and Aloxi 500 micrograms soft capsules, be updated to reflect the risk factors for developing QT prolongation on the grounds that QT prolongation is a recognised safety concern for the class, relevant post-marketing reports were included in the PSUR and this factor is also listed as a potential risk in the RMP. Moreover the PRAC recommended that the product information also reflect that hypokalaemia and hypomagnesaemia should be corrected prior to palonosetron administration. Therefore the current terms of the marketing authorisation should be varied[19].
- In the next PSUR, the MAH should comment on dose comparability between ondansetron and dolasetron with regards to effects on ECG parameters in clinical studies of chemotherapy-induced nausea and vomiting. This should be done in the consideration of the results of a QT-study conducted with ondansetron and in consideration of the withdrawal of dolasetron from the EU market (due to the risk of cardiac arrhythmias). In addition, the MAH should address in the next RMP several potential risks including severe hypersensitivity reactions and cardiovascular reactions.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted within 70 days of the data lock point.

6.19. Peginterferon alfa 2a - PEGASYS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Peginterferon alfa 2a is an antiviral used in the treatment of chronic hepatitis B and in the treatment of chronic hepatitis C under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Pegasys, a centrally authorised medicine containing peginterferon alfa-2a, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Pegasys (peginterferon alfa-2a) in the approved indication(s) remains favourable.

[19] The PRAC Assessment Report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should perform a cumulative review of cases of pulmonary hypertension as well as a comprehensive clinical evaluation of all reported cases of tongue hyperpigmentation and discuss the need to include this potential adverse effect in the product information.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted within 70 days of the data lock point.

*6.20. Pioglitazone – **ACTOS** (CAP), **GLUSTIN** (CAP)*

- Evaluation of PSUR procedures

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Background

Pioglitazone hydrochloride is a member of the thiazolidinedione class, used in the treatment of type II diabetes alone or in combination with other antidiabetic agents including metformin or glimepiride.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Actos and Glustin (centrally authorised medicines containing pioglitazone) and the combination products Tandemact (pioglitazone/glimepiride), Competact and Glubrava (pioglitazone/metformin) and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Actos and Glustin (and Tandemact, Competact and Glubrava see below 6.21. 6.22.) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisations.
- In the next PSUR, the MAH should address some aspects highlighted by PRAC including, among others: available data in relation to concomitant use of NSAIDs/coxibs and pioglitazone; full evaluation of a signal of blood dyscrasias in the light of recently published literature[20] on peroxisome proliferator-activated receptors (PPARs)γ and haematopoiesis; evaluation of the risk of bone fractures. The MAH should provide an explicit evaluation of the benefits and risks of concomitant use of pioglitazone with insulin in the elderly with particular focus on the risk of heart failure taking account of all available information. should focus on the elderly and use of pioglitazone in combination with insulin, and evaluation of this risk should be provided.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted within 70 days of the data lock point.

*6.21. Pioglitazone, glimepiride - **TANDEMACT** (CAP)*

- Evaluation of a PSUR procedure

[20] 2. Avagyan S, Aguilo F, Kamezaki K, Snoeck HW. Quantitative trait mapping reveals a regulatory axis involving peroxisome proliferator-activated receptors, PRDM16, transforming growth factor-β2 and FLT3 in hematopoiesis. Blood 2011; 118(23):6078-86.

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

See summary of recommendation point 6.20. A single PSUR assessment encompassing concerning pioglitazone, and fixed-combination products containing pioglitazone with metformin, pioglitazone with glimepiride and pioglitazone with alogliptin was performed.

6.22. Pioglitazone, metformin – COMPETACT (CAP), GLUBRAVA (CAP)

- Evaluation of a PSUR procedures

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

See summary of recommendation point 6.20. A single PSUR assessment encompassing concerning pioglitazone, and fixed-combination products containing pioglitazone with metformin, pioglitazone with glimepiride and pioglitazone with alogliptin was performed.

6.23. Pyronaridine, artesunate – PYRAMAX (Art 58)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

The combination pyronaridine and artesunate is an antimalarial medicine used to treat acute uncomplicated malaria due to Plasmodium falciparum or P. vivax.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Pyramax, a centrally authorised medicine containing pyronaridine and artesunate, and issued a recommendation on CHMP's positive scientific opinion.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Pyramax (pyronaridine / artesunate) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the maintenance of CHMP's positive scientific opinion.

The frequency of submission of PSUR should remain six monthly and the next PSUR should be submitted within 70 days of the data lock point.

6.24. Ribavirin – REBETOL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Ribavirin is an antiviral used to treat for the treatment of chronic hepatitis C in combination with other medicines.

Based on the assessment of the PSURs (adults and paediatric use), the PRAC reviewed the benefit-risk balance of Rebetol, a centrally authorised medicine containing ribavirin, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Rebetol (ribavirin) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should address some issues raised by the PRAC. These comprise, among others, a comparative analysis to be included on the safety profile of ribavirin as part of a dual therapy regimen versus a triple therapy regimen, including a more detailed analysis of the safety profile of ribavirin (dual versus triple therapy) in patients with advanced liver disease.
- In addition, the MAH was asked to review the long-term follow-up data on the reversibility of growth inhibition from study P01906 and for this to be reflected in the product information. This should be submitted to EMA without any delay.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted within 70 days of the data lock point.

6.25. Romiplostim – NPLATE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Background

Romiplostim is an Fc-peptide fusion protein used in the treatment for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Nplate, a centrally authorised medicine containing romiplostim, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Nplate (romiplostim) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSUR should remain once yearly and the next PSUR should be submitted within 70 days of the data lock point.

6.26. Rotavirus vaccine, live, attenuated – ROTARIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogne (BE)

Background

Rotavirus vaccine is used for the active immunisation of infants aged 6 to 24 weeks for the prevention of gastro-enteritis due to rotavirus infection.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Rotarix, a centrally authorised medicine containing rotavirus vaccine live attenuated, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Rotarix (rotavirus vaccine live attenuated) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should provide a review of the results of investigation of possible effects of co-administration with oral poliovirus vaccine on intussusception. In addition, the MAH should provide a cumulative review of cases of anaphylaxis.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted within 70 days of the data lock point; the EURD list should be updated accordingly.

6.27. Saxagliptin – ONGLYZA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Saxagliptin is an antidiabetic agent. Onglyza, a centrally authorised product containing saxagliptin, is indicated as an add-on to existing monotherapies with other agents in the treatment of type 2 diabetes.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Onglyza, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Onglyza (saxagliptin) in the approved indication(s) remains favourable.

- The PRAC recommended that the product information should be updated to reflect the adverse reaction "abdominal pain" with a frequency "unknown"[21]. The package leaflet should be updated accordingly. Therefore the current terms of the marketing authorisation should be varied[22].
- In the next PSUR, the MAH should also address some issues raised by the PRAC regarding, among other aspects: cases reporting palpitations, pancreatitis; continued close monitoring of 'hepatic disorders' and 'renal and urinary disorders' and 'cardiac disorders'.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted within 70 days of the data lock point.

*6.28. Sitagliptin, metformin – **EFFICIB** (CAP), **JANUMET** (CAP), **RISTFOR** (CAP), **VELMETIA** (CAP)*

- Evaluation of PSUR procedures

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

The combination sitagliptin, a DPP-4 inhibitor, and metformin, a biguanide, is used in the treatment of type 2 diabetes mellitus.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Efficib, Janumet, Ristfor and Velmetia, centrally authorised medicines containing sitagliptin and metformin, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Efficib, Janumet, Ristfor and Velmetia (sitagliptin / metformin) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should also address some issues raised by the PRAC. These include pemphigoid and rhabdomyolysis to be kept under close monitoring; a cumulative review of cases reporting rhabdomyolysis without concomitant statin use (see also minutes of the PRAC 3-5 September 2012) to be provided; a discussion on the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) study to be provided.

The frequency of submission of PSURs should remain every 3 years and the next PSUR should be submitted within 90 days of the data lock point; the EURD list should be updated accordingly.

*6.29. Sulesomab – **LEUKOSCAN** (CAP)*

- Evaluation of a PSUR procedure

[21] Section 4.8 of the SmPC
[22] The PRAC Assessment Report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Sulesomab is a radiopharmaceutical used for diagnostic imaging for determining the location and extent of infection/inflammation in bone in patients with suspected osteomyelitis, including patients with diabetic foot ulcers.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of LeukoScan, a centrally authorised medicine containing sulesomab, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of LeukoScan (sulesomab) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSUR should remain three-yearly and the next PSUR should be submitted within 90 days of the data lock point.

6.30. Telithromycin – KETEK (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Telithromycin is an antibacterial agent related to the macrolides and used in the treatment of mild to moderate community-acquired pneumonia, acute exacerbation of chronic bronchitis and acute sinusitis. It is also used in the treatment of tonsillitis/pharyngitis caused by *Streptococcus pyogenes* under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ketek, a centrally authorised medicine containing telithromycin, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Ketek (telithromycin) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should provide a cumulative review of events classified as renal failure or acute renal failure as well as a comprehensive review of cumulative events of convulsions, hypoesthesia and tremor.
- In addition, the MAH should provide within the next PSUR a thorough review and complete analysis of serious visual events; and a review of a possible drug- drug interaction between ritonavir and telithromycin.

- The MAH should continue to closely monitor several ADRs, including atrioventricular block and cardiac events.

The frequency of submission of PSUR should remain once yearly and the next PSUR should be submitted within 70 days of the data lock point.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of post-authorisation safety studies

7.1.1. **Alipogene tiparovec – GLYBERA** (CAP)

- Evaluation of a protocol for a PASS - pursuant an obligation imposed in accordance with Article 21a and 22a Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Glybera, a centrally authorised medicine containing alipogene tiparovec, is the first gene therapy product (ATMP) approved in the EU. It is indicated for treatment of adults with genetically confirmed lipoprotein lipase deficiency (LPLD) who experience severe or multiple pancreatitis attacks despite a low-fat diet.

The establishment of a disease registry, 'LPLD Registry' was proposed by the MAH in the context of the long-term safety and efficacy follow-up required as a condition of the MA. A PASS study protocol with the title 'An Observational Longitudinal Pharmacoepidemiologic Study in Lipoprotein Lipase-Deficient (LPLD) Patients, Either Treated or Not Treated with Alipogene Tipravovec (Glybera)', to be performed with the data from the registry, was presented for review by the PRAC.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 2012 1.0 - in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that the design of the study did not fulfil the study objectives.

The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 30 days-assessment timetable will be applied.

7.1.2. **Teduglutide – REVESTIVE** (CAP)

- Evaluation of a protocol for a PASS upon CHMP request - pursuant to an obligation imposed in accordance with Article 21a and 22a Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Background

Revestive, a centrally authorised product containing teduglutide, a recombinant GLP-2 analogue, is indicated as a treatment for adult patients with short bowel syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.

At the time of the marketing authorisation, the safety database of the MAH was limited since short bowel syndrome is an orphan disease. In order to further elucidate the potential and identified risks, as outlined in the RMP, a requirement to perform a non-interventional study to gather further safety data was requested. The MAH presented a protocol for an international retrospective/prospective, long-term observational, non interventional open cohort study of patients with SBS and no active malignancy.

The PRAC was requested to provide advice to CHMP on a protocol submitted by the MAH (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) to address this issue and assessed by the Rapporteur.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 2012 1.0 - in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that the design of the study did not fulfil the study objectives.

The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 90 days to the EMA. A 30 days-assessment timetable will be applied.

7.1.3. Telaprevir – INCIVO (CAP)

- Evaluation of a protocol for a PASS upon CHMP request – included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Incivo is a centrally authorised medicine containing telaprevir, an antiviral used in the treatment of genotype 1 chronic hepatitis C in selected patients in combination with peginterferon alfa and ribavirin.

As part of the RMP for Rash and Serious Cutaneous Adverse Reactions (SCARs), the MAH for Incivo (telaprevir), was required to conduct an educational programme amongst physicians treating hepatitis C on rash in order to mitigate the risk for SCARs (see also 9.1.1.). The MAH submitted a protocol for a study (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) for the evaluation of the effectiveness of the educational programme on rash which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for the assessment of the effectiveness of the education programme for Incivo (telaprevir) could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA before finalisation of the procedure.

8. Product related pharmacovigilance inspections

8.1. List of planned pharmacovigilance inspections

None

8.2. On-going or concluded pharmacovigilance inspection

The PRAC discussed the results of some inspections conducted in the EU. Disclosure of information on results of pharmacovigilance inspections could undermine the protection of the purpose of these inspections, investigations and audits. Therefore such information is not reported in the published minutes.

9. Other Safety issues for discussion requested by the CHMP or the EMA

9.1. Safety related variations of the marketing authorisation (MA)

9.1.1. Telaprevir – INCIVO (CAP)

- PRAC consultation on a safety-related type II variation upon CHMP request

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Telaprevir is an antiviral used in the treatment of in the treatment of genotype 1 chronic hepatitis C in selected patients, in combination with peginterferon alfa and ribavirin.

Severe cutaneous adverse reactions, including drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome (SJS), were recognised as side effects of Incivo (telaprevir) at the time of the marketing authorisation. They were considered in the benefit-risk assessment and appropriate information was included in the product information.

The CHMP is evaluating a type II variation for Incivo (telaprevir) to update the product information to reflect new information following 2 reported cases of toxic epidermal necrolysis (TEN). The CHMP requested PRAC advice on the assessment of this variation.

Summary of advice

- The MAH should provide further information (according to the list of questions agreed by the PRAC) on the management of peginterferon therapy in case of a severe telaprevir-associated rash, the appropriate concomitant use of other drugs that may cause serious cutaneous adverse reactions (SCAR), as well as clarification of the post-marketing reporting frequencies for SCAR entities (DRESS, SJS) before finalisation of the procedure at CHMP level.

9.2. Renewals of the Marketing Authorisation, Conditional Renewals and Annual Reassessments

9.2.1. Histamine dihydrochloride – CEPLENE (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Background

Ceplene is a centrally authorised medicine containing histamine dihydrochloride, indicated for the treatment of adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2).

Ceplene (histamine dihydrochloride) was authorised under exceptional circumstances in 2008 and the benefit-risk is reviewed on a yearly basis by the CHMP, based on the additional post-authorisation data (i.e. Specific Obligations) submitted. The PRAC is responsible for providing advice to the CHMP on this annual re-assessment with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available information on the status of the fulfilment of Specific Obligations and safety data submitted, the PRAC considered that the annual re-assessment procedure for Ceplene (histamine dihydrochloride) could only be finalised if satisfactory clarification is given on some pending issues. These include further information requested on the clinical trial titled “An open-label, multicenter study of the effects of remission maintenance therapy with Ceplene (histamine dihydrochloride), given in conjunction with low-dose interleukin-2 (IL-2, Proleukin), on immune response and minimal residual disease in adult patients with acute myeloid leukemia in first complete remission” ..

9.2.2. Pazopanib – VOTRIENT (CAP)

- PRAC consultation on a renewal procedure of the conditional marketing authorisation

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Votrient is a centrally authorised product containing pazopanib, a tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor (PDGFR)-α and –β, and stem cell factor receptor (c-KIT). It is indicated for the treatment of renal cell carcinoma (RCC) and soft tissue sarcoma (STS) in selected patients.

Votrient (pazopanib), was authorised under a conditional marketing authorisation in 2011. A request for renewal of the marketing authorisation was submitted by the MAH for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available information on the status of the fulfilment of Specific Obligations, the safety data submitted and the CHMP Rapporteur assessment report, the PRAC considered that a renewal of the conditional marketing authorisation could only be finalised if satisfactory clarification was given in response to some points raised by the PRAC regarding the adverse drug reactions observed in the clinical trial COMParing the efficacy, sAfety and toleRability of paZopanib vs. sunitinib (COMPAREZ) and the known safety profile for pazopanib.

9.2.3. Sugammadex – BRIDION (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Background

Bridion is a centrally authorised medicine containing sugammadex, a selective relaxant binding agent used in reversal of neuromuscular blockade induced by rocuronium or vecuronium.

The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the risk management system for Bridion (sugammadex), and the CHMP Rapporteur's assessment report, the PRAC concluded that no unaddressed safety concerns had arisen from the assessment of this first renewal procedure.
- However the procedure could only be finalised at CHMP level if the RMP version 5 is updated in accordance with the recommendations at point 4.3.4. (sugammadex - signal of respiratory symptoms).
- The frequency of submission of PSURs should remain every 3 years.

9.2.4. Trabectedin – YONDELIS (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Background

Yondelis is a centrally authorised product containing trabectedin, indicated for the treatment of selected patients with advanced soft tissue sarcoma and in combination with pegylated liposomal doxorubicin (PLD) for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

Yondelis (trabectedin) was authorised under exceptional circumstances in 2007. The benefit-risk is reviewed on a yearly basis by the CHMP, based on the additional post-authorisation data (i.e. Specific

Obligations) submitted. The PRAC is responsible for providing advice to the CHMP on this annual re-assessment with regard to safety and risk management aspects.

Summary of advice

Based on the review of the available information on the status of the fulfilment of Specific Obligations and safety data submitted, the PRAC considered that the annual re-assessment procedure for Yondelis (trabedectin) could be finalised at CHMP level.

9.3. Timing and message content in relation to MS safety announcements

None

9.4. Other requests

See also Telaprevir 7.1.3.

9.4.1. Iron containing medicinal products (solution for injection, intravenous use) (NAP)

- PRAC consultation on an Article 31 referral procedure upon CHMP's request

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)
PRAC Co-Rapporteur: Qun-Ying Yue (SE)

Background

The Referral under Article 31 of Directive 2001/83/EC was triggered by France for a benefit-risk review of intravenous (IV) iron-containing medicinal products due to safety concerns of allergic reactions and risk during pregnancy (see 'Start of community reviews CHMP meeting of 12-15 December 2011' EMA/968891/2011). The CHMP, conducting the assessment of this procedure started before the establishment of the PRAC, requested the advice of the PRAC on some aspects including approaches to further explore potential differences, especially between the estimated rates of reported severe allergic reactions among the different IV iron-containing medicines under review.

Summary of advice

- In order to allow review of any new serious cases the MAHs for the concerned products should be requested to submit to the EMA annual cumulative reviews of hypersensitivity case reports, all fatal cases and all pregnancy cases, together with usage data. These reports should be assessed cumulatively within the same timeframe.
- The MAHs should closely monitor cases of hypersensitivity with active follow-up of cases by targeted questionnaires and consideration should be given to the feasibility of obtaining more data, particularly regarding hypersensitivity reactions, in the form of a pharmacoepidemiological study; prospective data collection from national specialist centres, e.g. renal centres, should also be considered, given the expected concomitant administration of iron in iron-deficient chronic renal disease. The MAHs should provide feasibility assessments based on an analysis of relevant data sources.

9.4.2. Phentermine, topiramate

- PRAC consultation on an evaluation of an initial marketing authorisation procedure, upon CHMP's request

Background

On 18 October 2012, the CHMP adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Qsiva, intended for the treatment of obesity. The applicant requested a re-examination of the opinion. Upon CHMP request the PRAC provided advice, relating to risk management aspects, on the re-examination procedure.

Post-meeting note: after considering the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorisation on 21 February 2013 (see EMA Q&A EMA/109958/2013).

10. Other Safety issues for discussion requested by the Member States

10.1. Renewals of the Marketing Authorisation

None

10.2. Safety related variations of the marketing authorisation

See roxithromycin 4.3.1.

10.3. Other requests

10.3.1. Mycobacterium bovis BCG (Bacillus Calmette-Guerin) vaccine, Danish strain 1331, live attenuated - BCG VACCINE SSI (NAP)

- PRAC consultation on a stand-alone RMP procedure upon Member State's request

Regulatory details:

PRAC Rapporteur: *to be appointed*

Background

For background, see minutes of the PRAC 7-10 January 2013.

Following a discussion at the 7-10 January 2013 PRAC meeting, Denmark (DK) as reference member state for the BCG vaccine SSI presented an update on the issue, clarifying those aspects to be further investigated in relation to quality and manufacturing of the vaccine in order to address an increase in the reported rate of lymphadenitis in some countries, in order to finalise advice for possible improvement of to the RMP. A list of questions was discussed for the EMA CHMP Biologic Working Party[23] (BWP). Further advice on the RMP for BCG vaccine SSI will be agreed upon receipt of the responses. EMA will inform the PRAC on timelines for the receipt of responses.

The PRAC appointed Doris Stenver (DK) for follow-up action.

[23]The LoQ was agreed via written procedure on 12 March 2013

Post-meeting note: As of the 4-7 March meeting 2013 finalisation of the LoQ is pending. Further discussion will be planned for the April 2013 PRAC meeting.

11. Organisational, regulatory and methodological matters

11.1. Mandate and organisation of the PRAC

None

11.2. Pharmacovigilance audits and inspections

None

11.3. Periodic Safety Update Reports & Union Reference Date (EURD) List

11.3.1. Periodic Safety Update Reports

11.3.1.1. PSUR Single assessment

- Start of PSUR single assessment of substance contained in both CAPs and NAPs

The PSUR single assessment of substances contained in both CAPs and NAPs will start in April 2013, i.e. when the EURD list takes effect. These substances will be specifically identified in the EURD list and guidance will be provided to MAHs regarding the PSUR submission requirements to NCAs and EMA including the related procedure numbers. Prior to the March 2013 plenary meeting, EMA will provide the PRAC with the list of substances subject to a single assessment.

11.3.2. PSURs Repository

None

11.3.3. Union Reference Date List

11.3.3.1. Consultation on the draft List, version February 2013

EMA reported back from the discussion on the implementation of the pharmacovigilance legislation which took place at the EMA Management Board on 13 December 2012 (see Agenda of the EMA 78th meeting of the EMA Management Board B2c).

The EMA management board confirmed that single assessment of PSURs will not take place in 2013 for active substances that are only used in NAPs. This decision has an impact on the content of the EURD list which includes legally binding submission dates (through the data lock points (DLPs) agreed with the PRAC, CHMP and CMDh) for single assessment procedures of products subject to different MAs and authorised in more than one Member State. Therefore, the EURD list cannot yet contain substances that will not follow a single assessment.

The PRAC supported the proposal that substances with a DLP between 1 April 2013 and 31 March 2014, which are contained in NAPs only should not be included the EURD list (see post-meeting note 1). As a consequence, the PSURs will continue to be assessed at national level as per Article 107c(2) of the Directive 2001/83/EC. However, the PRAC also supported that PSURs should be requested in line with the DLP originally published in the EURD list, i.e. in 2013 and Q1 2014 as appropriate, and NCAs should consider to support continuation of PSUR assessments under the 'PSUR Work Sharing'.

Products authorised under Articles 10(1), 10a, 14 and 16a are by default still subject to a derogation from submitting a PSUR, except if required by a competent authority on the grounds laid down in Article 107b(3)b.

EMA clarified that PRAC advice on the EURD list for nationally authorised products is advice to the CMDh which is responsible for adoption, this advice will be further considered at the CMDh meeting in March 2013.

Post-meeting note I: following the PRAC meeting in February 2013, the scope of substances proposed to be temporally removed from the EURD list was extended to include those with a DLP between 1 April 2013 and 31 August 2014.

Post-meeting note II: the EMA presented at the remote teleconference on the organisational matters of the PRAC, on 21st February 2013, the outcome of the preliminary discussion on the amended list held at CMDh at their February 2013 meeting and further discussion is scheduled at their March 2013 meeting. In the meantime, the CMDh adopted the EURD list version February 2013 including the substances contained in NAPs only with a DLP between 1 April 2013 and 31 August 2014.

11.3.3.2. PSUR flowchart

The EMA secretariat presented a set of criteria for rationalising plenary discussion time relating to PSUR assessments at the meetings of the PRAC, in line with the most recent recommendations from the EMA MB on the need for careful management of resources (See minutes of the 77th meeting of the EMA MB). These criteria had been developed by the EMA in collaboration with Member States through the Governance structure for the implementation of the pharmacovigilance legislation. These criteria should be applied as of the March 2013 meeting.

The criteria, in establishing the need for plenary discussion, take into consideration different factors according to the outcome of the PSUR assessment such as a recommendation for variation, suspension or revocation of the MA, a request for additional risk minimisation measures and pharmacovigilance activities as well as divergent comments and disagreements that cannot be resolved within the updated PRAC Rapporteur assessment report. Other PSUR assessments where the maintenance of the MA is recommended will not require discussion at the PRAC plenary.

11.4. Signal Management

11.4.1. Signal Management

- Feedback from Signal Management Review Technical (SMART) Working Group

Item deferred to the next meeting.

11.5. Adverse Drug Reactions reporting and additional reporting

11.5.1. Management and Reporting of Adverse Reactions to Medicinal Products

None

11.5.2. Additional Monitoring

None

11.5.3. List of Product under Additional Monitoring

11.5.3.1. Update on Creation and maintenance of the List

EMA informed the PRAC that a NUI will be circulated to MSs with the aim of supplementing information received through a previous NUI in order to finalise the list of medicinal products which are subject to additional monitoring for adoption at the PRAC. An update will be present at March 2013 PRAC meeting.

Post-meeting note: a NUI was circulated by EMA on 12 February 2013.

11.6. EudraVigilance Database

11.6.1. Activities related to the confirmation of full functionality

None

11.6.2. Changes to EudraVigilance Database and functional specifications

None

11.7. Risk Management Plans and Effectiveness of risk Minimisations

11.7.1. Risk Management Systems

None

11.7.2. Tools, Educational Materials and Effectiveness Measurement for Risk Minimisation

- Guideline on good pharmacovigilance practices (GVP) Module XV on Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators

This item was discussed at the remote teleconference of the organisational matters of the PRAC on Thursday 21 February 2013. EMA outlined comments received from the members on the draft GVP Module XV. Clarifications were requested on the role of the Agency, some definitions included, the role of NCAs and transparency provision. The PRAC recommended ensuring coordination with parallel CIOMS Working Group IX initiatives. EMA will circulate a revised version to be published by the EMA for public consultation.

11.8. Post-authorisation Safety Studies

None

11.9. Community Procedures

None

11.10. Interaction with EMA Committees and Working Parties

11.10.1. Committees

11.10.2. Paediatric Committee (PDCO)

- Project for collection of pregnancy data for new or commonly used drugs during pregnancy

This item was presented at the remote teleconference of the organisational matters of the PRAC on Thursday 21 February 2013. EMA presented the scope of a cross committee project aiming at identification and filling-in of potential gaps and the establishment of systematic processes to document selection of medicinal products requiring collection of pregnancy data. A call to all committees was launched to participate in the project and currently 2 members of the PRAC are providing input to a draft of a concept paper under development. The PRAC noted the discussion that took place at the 10th ENCePP Plenary Meeting (see Agenda) on maternal medication and pregnancy outcomes and different study designs for signal detection and signal evaluations in pregnancy. It underlined the importance of coordination and exchanging views. Furthermore the PRAC commented that an additional GVP module on the subject could be a useful tool to provide guidance in this important field. A further update will be given to the PRAC before release of the concept paper for public consultation.

11.10.3. Working Parties

None

11.11. Interaction within the EU regulatory network

None

11.11.1. Implementation of the pharmacovigilance legislation: feedback from the EMA Management Board dated December 2012

This item was discussed at the remote teleconference of the organisational matters of the PRAC on Thursday 21 February 2013. The PRAC received an update on the outcome of the implementation of the pharmacovigilance legislation which took place at EMA Management Board on 13 December 2012 (see Agenda of the EMA 78th meeting of the EMA Management Board B2c).

11.12. Contacts of the PRAC with external parties and interaction of the EMA with interested parties

11.12.1. Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

None

11.12.2. Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study

- Transfer of the evaluation of the D:A:D data and responsibility for regulatory representation in the HAART Oversight Committee

Following the discussion at the January 2013 meeting the PRAC discussed the representation of the PRAC in the HAART Oversight Committee and EMA informed that a call for candidates will be launched in 4-7 February 2013 for appointment at the 4-7 March 2013 PRAC meeting.

A letter from PRAC/EMA in response to the HAART OC letter will be prepared following nominations. The PRAC recommended the next updates of the RMPs for antivirals medicines to be submitted for assessment by the PRAC make clear the contribution of D:A:D to fulfilling pharmacovigilance requirements. A proposal for a strategic implementation of this recommendation will be prepared by the EMA.

Post-meeting note: deadline for nominations by Tuesday 26 February 2013 EOB.

11.12.3. Others

- Proposals for drug safety priorities for EC DG Research Framework Programme 8 (FP8) funding in Work Programme 2014

The finalised list of drug safety topics for forwarding to the European Commission as priorities for possible funding in the Framework Programme 8 (FP-8) 1st Call (2014 work programme) was adopted.

12. Any other business

12.1. Overview of cases of progressive multifocal leukoencephalopathy (PML) in EudraVigilance

- Presentation of the overview and next steps

An overview of all reports of progressive multifocal leukoencephalopathy (PML) received in EudraVigilance was presented to the Committee. This included the reporting trends over the years for all reports of PML, for reports of cases with a fatal outcome, numbers of reports for most frequently reported drugs and a disproportionality analysis.

Based on the overview the PRAC discussed the possible next steps. A broader discussion was initiated on the opportunity to develop an evidence-based strategy for regulatory action, following investigation of potential signals of PML (adherence to a case definition, exclusion of confounders etc.), with the view of managing this risk through different risk minimisation measures.

The EMA will draft a proposal for an evidence-based strategy, with the input of PRAC members who expressed their interest.

ANNEX I – List of abbreviations

For a List of the abbreviation used in the PRAC minutes, see:

www.ema.europa.eu

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ANNEX II – List of participants: *including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 4-7 February 2013 meeeting.*

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product / substance
Bettina Schade	Austria	Full involvement	
Jean-Michel Dogne	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	Telmisartan, hydrochlorothiazide
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Christos Petrou	Cyprus	Full involvement	
Eva Jirsova	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Evelyne Falip	France	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
George Aislaitner	Greece	Full involvement	
Julia Pallos	Hungary	Full involvement	
Gudrun Kristin Steingrimsdottir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Fernanda Ferrazin	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjorg Buajordet	Norway	Full involvement	
Pernille Harg	Norway	Full involvement	
Margarida Guimaraes	Portugal	Full involvement	
Alexandra Pego	Portugal	Full involvement	
Nicoalae Fotin	Romania	Involvement in discussions only with respect to procedures involving the following products i.e. no part in final deliberations and voting as appropriate as regards to these medicinal	Roxithromycin Tobramycin Telithromycin

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product / substance
		products. Cannot act as Rapporteur or Peer-reviewer for:	
Tatiana Magalova	Slovakia	Full involvement	
Gabriela Jazbec	Slovenia	Full involvement	
Milena Radoha-Bergoc	Slovenia	Full involvement	
Miguel-Angel Macia	Spain	Full involvement	
Dolores Montero	Spain	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Ulla Wandel Liminga	Sweden	Full involvement	
Julia Dunne	United Kingdom	Full involvement	
June Munro Raine	United Kingdom	Full involvement	
Julie Williams	United kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies Product / substance
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise (Marieke) De Bruin		Cannot act as Rapporteur or Peer-reviewer for:	Rotavirus vaccine, live, attenuated, Axitinib, Fesoterodine, Sunitinib,
Stephen Evans		Cannot act as Rapporteur or Peer-reviewer for:	Rotavirus vaccine, live, attenuated
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Cannot act as Rapporteur or Peer-reviewer for:	Agomelatine
Lennart Waldenlind		Full involvement	

Additional European experts participating at the meeting for specific Agenda items	Country	
Veerle Verlinden	Belgium	
Benedicte Lunddahl Rasmussen	Denmark	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Radhakrishnan Rajaratnam	Finland	
Veronique Tonnay	France	
Christine Diesinger	Germany	
Jutta Krappweis	Germany	
Valerie Strassman	Germany	
Maria Grazi Evandri	Italy	
Daniela Melchiorri	Italy	
Anna Rita Meneguz	Italy	
John J Borg	Malta	
Kamila Czajkowska	Poland	
Charlotte Backman	Sweden	
Kristina Dunder	Sweden	
Filip Josephson	Sweden	
Karl-Mikael Kälkner	Sweden	
Hans Sjögren	Sweden	
Phillip Bryan	United Kingdom	
Nicola Parkinson	United Kingdom	
Catherine Tregunno	United Kingdom	
Jane Woolley	United Kingdom	

Observer from the European Commission
Helen Lee - DG Health and Consumers
European Medicines Agency
Peter Arlett - Head of Sector for Pharmacovigilance and Risk Management
Roberto De Lisa - Scientific Administrator, PRAC Secretariat
Zaide Frias - Scientific Administrator, Regulatory Affairs
Georgy Genov – Section Head, Signal Detection and Data Analysis
Ana Hidalgo-Simon – Section Head, Risk Management
Anthony Humphreys – Head of Sector for Regulatory Affairs and Organisational Support
Sheila Kennedy – Section Head, Scientific Committee Support
Kasia Kmiecik – Assistant, PRAC Secretariat
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